

JCS80 U.S. PTO
11/25/98

PC9873AJTU

JCS49 U.S. PTO
09/20/19
86/55/11
11/25/98

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of

Inventor: **Imran Ahmed**

For: **Method Of Treating Eye Infections With Azithromycin**

Enclosed are also:

- ☐ ___ sheets of drawing(s).
- ☐ An assignment of the invention to PFIZER INC. (\$40.00)
- ☐ A certified copy of a _____ application.
- ☒ A Declaration (also includes Power of Attorney).
- ☐ A Disclosure Statement, Form FB-A820 and copy(ies) of the reference(s) cited.
- ☒ This application is based on United States Provisional Application No. 60/067,250, filed on December 2, 1997, the priority of which is hereby claimed.
- ☒ Preliminary Amendment
- ☐ This application is being filed without a Declaration and Power of Attorney.
- ☒ The undersigned attorney/agent has been authorized to file the subject application on behalf of the inventor(s). All correspondence should be sent to GREGG C. BENSON, Pfizer Inc., Eastern Point Road, Groton, CT 06340.

09200419-112598

ADDRESS MAIL NO. EE 27978276645

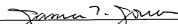
CLAIMS AS FILED

<u>FOR</u>	<u>NUMBER FILED</u>		<u>NUMBER EXTRA</u>	<u>RATE</u>	<u>BASIC FEE \$760.00</u>
Total Claims	<u>7</u>	-20 =	<u>0</u>	X \$18.00	<u>0.00</u>
Independent Claims	<u>2</u>	- 3 =	<u>0</u>	X \$78.00	<u>0.00</u>
Multiple Dependent Claim(s) fee (\$260.00)					<u>0.00</u>
Total Filing Fee					<u>\$ 760.00</u>

[X] Please charge Deposit Account No. 16-1445 in the amount of **\$760.00**. Two copies of this sheet are enclosed.

[X] The Commissioner is hereby authorized to charge any additional fees which may be required under 37 C.F.R. 1.16 and 1.17 by the filing of this paper, or credit any overpayment, to Deposit Account No 16-1445. Two copies of this sheet are enclosed.

Date: November 25, 1998


James T. Jones
ATTORNEY for Applicant
Reg. No. 30,561

Pfizer Inc.
Patent Department
Eastern Point Road
Groton, CT 06340
(860) 441-4903

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Imran Ahmed

SERIAL NO.: To Be Assigned : Examiner: To Be Assigned
: Art Unit: To Be Assigned

FILED: HERewith :

FOR: Method Of Treating Eye
Infections With Azithromycin

Assistant Commissioner For Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Please amend the application as follows:

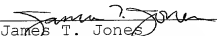
Enter the following sentence as the first paragraph
following the title:

-- This application is filed claiming priority
from co-pending Provisional Application No. 60/067,250
filed December 2, 1997. --

A Notice of Allowance is courteously solicited.

Respectfully submitted,

Date: November 25, 1998


James T. Jones
Attorney for Applicant
Reg. No. 30,561

Pfizer Inc
Patent Department
Eastern Point Road
Groton, CT 06340
(860) 441-4903

EXPRESS MAIL NO. 66 279 78 2766 US

Method Of Treating Eye InfectionsWith AzithromycinField of the invention

- 5 This invention relates to methods of treating eye infections by topically administering azithromycin to an eye of an animal in need of such treatment.

Background of the invention

- 10 Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antimicrobial compound derived from erythromycin A. Azithromycin is disclosed in U. S. patent no. 4,474,768 to Bright and U.S. patent no. 4,517,359 to Kobrehel et al. These patents disclose that azithromycin and certain derivatives thereof possess antibacterial properties and are accordingly useful as antibiotics.
- 15 Azithromycin is commonly administered orally, in a number of different dosage forms such as tablets, capsules, and suspensions, for the treatment of antibacterial infections. Until the present invention, however, azithromycin was not known to be effective when topically administered to the eye. Azithromycin is known to be effective for the treatment of eye infections in
- 20 humans when administered systemically, e.g., orally. However, it is also known that antibiotics which are effective when administered by a systemic route are not necessarily effective when applied topically, directly to the eye. For example, it has been reported that when tetracyclines are applied to the cornea, they do not penetrate the intact normal cornea even though they are
- 25 able to diffuse into spinal fluid and into ocular fluids if the systemic dose is high enough (Douvas MG, et al, Arch Ophthalmol. 46:57, 1951).

09200339-112508

Summary of the invention

This invention provides a method of treating an ocular infection, comprising topically administering, to an eye of an animal, including man, in need of such treatment, an ocular infection-treating amount of azithromycin.

- 5 Topical administration means the application, directly to the surface of an eye, of azithromycin in a composition comprising azithromycin and a pharmaceutically acceptable topical carrier. In a preferred embodiment, the composition is applied directly to an eye as a single dose (equivalent to approximately 5mg) per day for five days. It is noted that a "single dose"
- 10 means the amount for a single eye.

- The invention further provides pharmaceutical compositions for topical application directly to an eye of an animal, including a human, said compositions being suitable for the treatment of an ocular infection, comprising azithromycin and a pharmaceutical vehicle suitable for topical
- 15 application, wherein said azithromycin is at a concentration in said vehicle sufficient to remediate said ocular infection. In a preferred embodiment, the concentration of azithromycin in the vehicle is such that a single dose (approx. 5mg per eye) of said composition administered once daily for five days remedies the infection. The capability of achieving once-a-day topical
- 20 dosing with azithromycin was highly unexpected considering that most drugs are rapidly cleared from the precorneal area by tear drainage. Thus, commonly most topical regimens using known antibiotics such as gentamycin and erythromycin must be administered frequently with application rates of 4-6 times daily sometimes being required to produce effective drug levels in target
- 25 ocular tissues. Topical formulations of azithromycin, by contrast, achieve relatively high and sustained levels in ocular tissues including cornea, conjunctiva, lids, and sclera. Because of the excellent penetration of azithromycin into ocular tissues, patient compliance is expected to be significantly enhanced by virtue of this invention.

The types of ocular infections treatable through the topical administration of azithromycin broadly include any eye infection caused by a bacterial species known to be amenable to systemic treatment with azithromycin. In particular, the invention is applicable to the treatment of

5 trachoma, a chronic follicular conjunctivitis due to *Chlamydia trachomatis*, the world's leading cause of preventable blindness.

Detailed description

The term "azithromycin" includes the pharmaceutically acceptable salts thereof, and anhydrous as well as hydrated forms. The azithromycin is preferably present as the dihydrate, disclosed, for example, in published European Patent Application 0 298 650 A2 and in co-pending U. S. application 07/994,040 filed December 21, 1992, each of which is herein incorporated by reference.

10

Compositions (sometimes referred to herein as "formulations") according to the invention comprise azithromycin and a pharmaceutically acceptable vehicle suitable for topical application to an eye. Azithromycin (calculated using the dihydrate) is typically present in the composition at a concentration of 0.1 to 2.5 weight % (w/w), usually 0.2 to 2.0 weight %, based

15

20 on the weight of the composition. A preferred concentration is 0.5 weight %.

The compositions can include a preservative if desired, although preferred compositions do not contain a preservative. The compositions can also optionally contain surfactants, viscosity enhancers, buffers, sodium chloride, and water to form aqueous sterile ophthalmic solutions and suspensions. In order to prepare sterile ophthalmic ointment formulations,

25

azithromycin is combined with an appropriate vehicle such as mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations containing azithromycin can be prepared by suspending azithromycin in a hydrophilic base prepared from a combination of, for example, a carboxyvinyl

30

polymer sold under the designation Carbopol® (registered trademark of the B.

F. Goodrich Company for a series of such polymers) according to published formulations for analogous ophthalmic preparations. Tonicity agents may also be incorporated in such gel formulations.

5 Azthromycin can be formulated as an ophthalmic solution in isotonic saline using glycerine as an isotonicity agent. A preservative can optionally be included as an excipient. Such ophthalmic solutions also include a pharmaceutically acceptable buffering agent, typically a combination of boric acid and sodium borate, sufficient to maintain the pH of the solution between 7 and 8.

10 A preferred composition is 0.5 % w/w azithromycin dihydrate suspended in an inert, non-allergenic, preservative-free vehicle consisting of white petrolatum (55% w/w), mineral oil (42.5% w/w), and lanolin (2% w/w).

The invention is further disclosed by means of the following non-limiting examples. In the examples, reference to "water" means sterile water, suitable for use as water for injection.

15

Example 1

A preferred embodiment was prepared by incorporating 5g of azithromycin dihydrate into 995 g of a sterile vehicle comprising 55% by weight of petrolatum, 43% by weight of light mineral oil, and 2% by weight of lanolin. The procedure involved first heating an excess amount of the ointment vehicle of the aforementioned composition to 70°C in a glass vessel to produce a melt. In the next step, 995g of the molten sterile ointment was transferred into a compounding vessel equipped with a mixer and 5g of the azithromycin hydrate was added to the melt under agitation at 70°C to form a suspension. The azithromycin containing ointment was rapidly cooled by placing the compounding vessel in an ice bath. The "0.5% azithromycin ointment" was then filled into 1cc unit dose plastic syringes for dose application. This ointment may be sterilized by gamma radiation using a cobalt-60 source.

20

25

09200119 112558

Example 2

A 0.5 weight percent azithromycin dihydrate ophthalmic solution is prepared by dissolving 50g of azithromycin dihydrate (0.5 weight %), 67.0 g (0.67 weight percent) boric acid, 20.7 g (0.207 weight percent) sodium borate decahydrate, 100 g (1.0 weight percent) glycerin, 100 g of polyethylene glycol 300 (1.0 weight percent), and 0.40 g (0.004 weight percent) thimerosal (as a preservative) in about 8000 g of deionized distilled water. The pH is adjusted to 7.2 with HCl and NaOH. The final batch weight is brought to 10,000 g with the addition of the required amount of water. The final solution is filtered through a 0.2 micron Millipore filter and filtered into vials.

Example 3

In a preferred embodiment, an approximate 0.5 weight percent azithromycin dihydrate ophthalmic suspension is prepared as follows: 600 g of petrolatum is heated to 90°C for 2 hours in a jacketed 316 stainless steel vessel. The temperature is then decreased to 60°C. Light mineral oil, 350 g, is added to the petrolatum under mild agitation. The solution is passed through a sintered glass filter. Azithromycin dihydrate, 5g, is dispersed into the mineral oil/petrolatum solution under agitation to form a finely dispersed suspension. The suspension is cooled under slow agitation to form a semisolid suspension. The suspension is filled into plastic, polypropylene tubes and sterilized by gamma radiation using a cobalt-60 source.

Example 4

A 0.5 weight percent azithromycin dihydrate ophthalmic suspension is prepared as follows: 600 g of PEG 4000 is heated to 90°C for 2 hours in a jacketed 316 stainless steel vessel. The temperature is brought down to 60° C. PEG 400, 350 g, is added to the petrolatum under mild agitation. The solution is passed through a sintered glass filter. Azithromycin dihydrate, 50 g,

is dispersed into the PEG 4000/PEG 400 solution under agitation to form a finely dispersed suspension. The suspension is cooled under slow agitation to form a semisolid suspension. The suspension is filled into plastic, polypropylene tubes and sterilized by gamma radiation using a cobalt-60 source.

EXAMPLE 5

- 10 The following gel is prepared under strictly aseptic conditions:

	<u>% w/w</u>
Azithromycin Dihydrate	3.50
Chlorbutol BP	0.50
15 Carbopol® 934P	2.50
NaOH (4% w/v solution)	6.21
Water	87.29

- 20 Azithromycin dihydrate is dispersed in the sterile unneutralised Carbopol in water containing chlorbutol BP in solution. A sterile 4% w/v sodium hydroxide solution is then added with constant mixing to a final pH of 4-6.

EXAMPLE 6

- 25 The following ingredients are formed into a mixture:

	<u>% w/w</u>
Azithromycin Dihydrate	3.50
30 Chlorbutol BP	0.50
Citric acid monohydrate**	0.117
Sodium citrate dihydrate**	0.112
Sodium citrate 1% solution**	qs

Hydroxypropylmethylcellulose	
2906 USP 4000 cps (sterile)	3.80
Water	to 100.00
** buffers	

5

Citric acid, sodium citrate and chlorbutol BP are dissolved in 95% of the total water and the solution sterilized. Azithromycin powder is dispersed in the solution at ambient temperature using a high shear mixer. The hydroxypropylmethylcellulose, previously sterilized, is dispersed in the suspension and then allowed to hydrate over a period of about 15 minutes. The pH is adjusted to between 4-6 with a 1% solution of sterilized sodium citrate. The gel is adjusted to final weight with water and mixed thoroughly.

10

EXAMPLE 7

15

The following suspension, gelling in situ at body temperature, is prepared:

	<u>% w/w</u>
Azithromycin Dihydrate	3.50
20 benzalkonium chloride BP	0.02
citric acid monohydrate	0.117
sodium citrate dihydrate	0.112
Pluronic® F127**	19.00
sodium citrate/citric acid solution	qs
25 water	to 100.00

** Pluronic® F127 is a polyoxyethylene-polyoxpropylene block copolymer of average molecular weight about 11,500

30

Citric acid, sodium citrate and benzalkonium chloride are dissolved in 98% of the total water. The Pluronic® F127 is dispersed in this solution and left to hydrate overnight. The preparation is then thoroughly mixed and the pH adjusted to 4-6 with sodium citrate or citric acid solution as appropriate. The

solution is made to 96.5% of the total weight and sterile filtered into a sterile container. Azithromycin is dispersed aseptically in the filtered solution using a high shear mixer.

5

EXAMPLE 8

The following gel is prepared under strictly aseptic conditions:

	<u>% w/w</u>
10 Azithromycin Dihydrate	3.50
chlorbutol BP	0.50
ethylene maleic anhydride resin (EMA)	
type 91 (sterile)	0.80
dilute ammonium hydroxide solution	
15 (1.75% NH ₃)	4.40
water	90.80

20 The sterile EMA resin is dispersed in 50% of the total water, dilute ammonium hydroxide solution is stirred in and the mixture is heated at 95°C for 15 minutes. The resultant gel is allowed to cool to below 60°C.

The chlorbutol BP is dissolved in the remaining 50% of the water, at a temperature not exceeding 60°C, and sterile filtered into the gel which is mixed slowly.

Azithromycin is thoroughly dispersed in the gel.

25

What is claimed is:

1. A method of treating an ocular infection, comprising topically administering to an eye of an animal in need of such treatment an ocular infection-treating amount of azithromycin.
- 5 2. A method as defined in claim 1 wherein said azithromycin is present in a composition comprising a pharmaceutically acceptable topical vehicle at a concentration of from 0.1 to 2.5 weight percent.
- 10 3. A method as defined in claim 2, wherein said composition is administered once daily.
4. A composition for topical application directly to an eye of an animal, including a human, said composition being suitable for the treatment of an
- 15 ocular infection, comprising an effective amount of azithromycin in a pharmaceutical vehicle suitable for topical application to the eye.
5. A composition as defined in claim 4, wherein said azithromycin is present in a range of from 0.1 to 2.5 weight %.
- 20 6. A composition as defined in claim 4, wherein said azithromycin is present in an amount of 0.5 weight %.
7. A composition as defined in claim 4, wherein said composition is 0.5 %
- 25 w/w azithromycin dihydrate suspended in an inert, non-allergenic, preservative-free vehicle comprising white petrolatum (55% w/w), mineral oil (42.5% w/w), and lanolin (2% w/w).

ABSTRACT

The invention features methods and compositions for treating ocular infections. The method comprises topically administering to an eye of an animal in need of such treatment an ocular infection-treating amount of

5 azithromycin.

[illegible]

DECLARATION FOR PATENT APPLICATION

Docket Number (Optional)
PC9873A/JTJ

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled Method Of Treating Eye Infections With Azithromycin, the

specification of which is attached hereto unless the following box is checked:

☐ was filed on _____ as United States Application Number or PCT International Application Number: _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s), for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applicant(s)

Priority Not Claimed

(Number)	(Country)	(Day/Month/Year Filed)	<input type="checkbox"/>
(Number)	(Country)	(Day/Month/Year Filed)	<input type="checkbox"/>

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

(Application Number)	(Filing Date)
60/067,250	December 2, 1997

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)
----------------------	---------------	---

(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)
----------------------	---------------	---

I hereby appoint the following attorney(s) and/or agents(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Address all telephone calls to: James T. Jones at telephone number: 860-441-4903

Address all correspondence to: Patent Department
Pfizer Inc.
Eastern Point Road
Groton, CT 06340

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor (given name, family name) Imran Ahmed

Inventor's signature	Date
<u>[Signature]</u>	<u>Nov. 24, 1998</u>
Residence	Citizenship
<u>32 Cardinal Road</u>	<u>USA</u>
Post Office Address	
<u>32 Cardinal Road, East Lyme, CT 06333</u>	

Full name of second joint inventor (given name, family name)

Second inventor's signature	Date
Residence	Citizenship
Post Office Address	

☐ Additional inventors are being named on separately numbered sheets attached hereto.

Burden Hour Statement: This form is estimated to take 4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistance Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-0032), Washington, DC 20503. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231

I Declare, 4/97

EXPRESS MAIL NO. EE279782766US